UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,158	12/05/2001	Wu-Bo Li	0942.4750003	3737

26111 7590 09/20/2004

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 09/20/04 BA

Office Action Summary	Application No.	Applicant(s)	
	10/002,158	LI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57 and 59-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57 and 59-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of amendments and terminal disclaimers, filed 06/25/2004. Applicant has cancelled claim 58 is cancelled and presented new claim 67, thus claims 49-57 and 59-67 are pending and under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn. As new grounds of rejection are set forth, this action is NON-FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. **Claims 49-55, 57, 59-61, 63, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lachenmeier et al. (Biotechniques, 1992;13(1):124-31; see whole document), and Pruitt (Gene, 1988; 66:121-34; see whole document) and further in view of Rubenstein et al. (Nuc. Acids Res. 1990; 18(16):4833-4842; see whole document).**

The claims are directed to a process of recovering one or more circular single-stranded target nucleic acid molecules (e.g. ssDNA), where haptenylated probes hybridize to complementary target sequences and the probe-target complex is bound to a hapten-specific ligand conjugated to a matrix. Single-stranded target nucleic acids are subsequently treated to produce double-stranded DNA molecules (dsDNA). That dsDNA can be subjected to conditions, which denature dsDNA into ssDNA, is interpreted as broadly as reasonable to mean any condition *in vitro* or *in vivo* that results in ssDNA being derived from dsDNA.

Lachenmeier et al. teach a method of recovering circular single-stranded target nucleic acid molecules. More particularly, the single-stranded nucleic acid targets comprise of a mixture of M13 phage clones, containing target sequences as well as a Lac Z region (i.e. DNA molecules). (e.g. p. 124, Fig. 1; p. 126; Table 1). By using a probe with the specific sequence (Lac Z), the likelihood of random hybridization is reduced. Furthermore, the target molecules are enriched using a biotinylated probe and streptavidin-conjugated magnetic beads. (e.g. p. 124, Fig. 1; p. 126, col. 1, last ¶ bridging to col. 2, ¶ 1). In obtaining ssDNA using M13 phagemid, an intrinsic property for M13 replication in bacteria is that a dsDNA form occurs in the bacterial host, thus requiring specific conditions (e.g. culturing techniques), which result in ssDNA isolation. Lachenmeier does not explicitly teach that the isolated M13 target molecules can be

subsequently treated to produce double stranded DNA and that such DNA is then transformed into host cells.

Pruitt teaches a method of enriching clones whereby the clones are in the form of single-stranded DNA, and are isolated by hybrid selection where the hybrid is recovered because a specific probe DNA is bound to a column. (e.g. Abstract). More particularly, Pruitt teaches that the library of plasmids is constructed using M13 vectors (e.g. p. 123, col. 2, ¶ 1), and that libraries of single-stranded circular DNA are isolated (e.g. p. 124, col. 2, ¶ 3) through hybridization with specific sequences with matrix-bound probe sequences (e.g. p. 125, col. 1 ¶ 1). Pruitt teaches washing/incubating with various hybridization buffers and at elevated temperatures, such steps undertaken to ensure specific binding of target to probe sequences (i.e. reduce random hybridization). (e.g. p. 125, bottom full ¶, bridging to col. 2, ¶ 1). Pruitt teaches transformation of bacterial host using the isolated ssDNA, thus does not explicitly teach conversion of ssDNA into dsDNA (claim 49(D) and 50).

Rubenstein et al. teach a method of recovering single-stranded target nucleic acids using phagemids (i.e. M13 phagemid vector) containing target sequences (e.g. Abstract). As in the preceding references, single-stranded DNA is biotinylated and hybridized with ssDNA (e.g. p. 4834, col. 2, ¶ 2). In addition, ssDNA is converted to dsDNA prior to bacterial transformation (e.g. p. 4835, col. 1, ¶ 3; p. 4841, col. 1, ¶ 5). Furthermore, it is taught that both ssDNA and dsDNA can be used for transformation (p. 4841, col. 2, ¶ 2).

The ordinary skilled artisan seeking to develop a method for recovering ssDNA molecules from a mixture of such molecules, would have been motivated to combine the teachings of Lachenmeier et al. of recovering ssDNA using hybridization to a haptenylated probe

and ligand-conjugated matrix, with the teachings of Pruitt and Rubenstein et al., teaching routine techniques of using optimum hybridization conditions, as well as using plasmid or phagemid cloning comprising a library of target sequences. Furthermore, it would have been a routine matter to convert ssDNA into dsDNA prior to transformation with the added benefit of increased transformation efficiency, due to increased structural stability inherent in dsDNA as compared to ssDNA. It would have been obvious for the skilled artisan to convert the ssDNA recovered by Lachenmeier et al to dsDNA as taught by Rubenstein et al. so as to propagate and obtain a quantity of DNA molecules for future manipulation and study, because hybridization conditions for ssDNA molecules and conversion of ssDNA to dsDNA were well known techniques at the time of invention. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of the Applicants' invention, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

2. **Claims 49-57, 59-63, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lachenmeier et al., Pruitt, Rubenstein et al. and further in view of Rubenstein et al. (Nuc. Acids Res. 1990; 18(16):4833-4842; see whole document) and further in view of Rigas et al. (Proc. Natl. Acad. Sci. 1986; 83:9591-9595; see whole document) .**

Additional embodiments are directed to circular target nucleic acids being cosmids and that probes used contain degenerate sequences. Lachenmeier et al., Pruitt and Rubenstein et al. do not explicitly teach that in a method of screening a mixture of circular ssDNA that cosmids

can contain the nucleic acid molecules or that avidin can be substituted as the ligand that binds biotin.

Rigas et al. teach a method for rapidly screening a plasmid library using biotinylated probes (e.g. Abstract; p. 9592, Fig. 1). More particularly, Rigas et al. teaches that the method can be applied to cosmids and phage. (e.g. Abstract; p. 9595, col. 2, last ¶). In addition, Avidin is taught as a substitute ligand for Streptavidin (e.g. p. 9591, col. 2, ¶ 3).

At the time of the invention it would have been prima facie obvious for one of ordinary skill in the art to substitute a streptavidin equivalent, avidin, for binding biotin, as implicitly provided in Rigas which used both interchangeably. In addition, that a cosmid could be substituted for a plasmid or an M13 (i.e. phage) to contain nucleic acid sequences (e.g. library) was well known at the time of invention. One would have been motivated to modify the process of screening a library as taught Lachenmeier et al., Pruitt and Rubenstein et al. with using a cosmid to obtain the benefit of a vector containing larger sized sequences and avidin to expand the range of available ligands that can be conjugated to a matrix, in a rapid screening process. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of the Applicants' invention, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

3. **Claims 49-55, 57, 59-61, 63-66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lachenmeier et al., Pruitt, Rubenstein et al. and further in view of Rubenstein et al. (Nuc. Acids Res. 1990; 18(16):4833-4842; see whole document) and further in view of Symons (US 4,898,951; see whole document).**

Additional embodiments are directed to the method where the ligands that bind biotin are antibodies. Lachenmeier et al., Pruitt and Rubenstein et al. do not explicitly teach that in a method where antibodies are used instead of streptavidin.

Symons teaches anti-biotin antibodies as art-recognized equivalents to avidin or streptavidin for binding to biotin (e.g. col. 14, ll. 10-15).

At the time of invention, it would have been prima facie obvious for one of ordinary skill in the art to substitute an equivalent to avidin or streptavidin, including the antibodies against biotin and functional fragments thereof, for binding in a method as taught by Lachenmeier et at., Pruitt and Rubenstein et al. An express suggestion to substitute one equivalent component or process for another is not necessary to render such a substitution obvious. It follows, that given the nature of the components being substituted and the knowledge in the art, there would have been a reasonable expectation of success in substituting antibodies as the ligands to bind biotin.

4. **Claims 49-55, 57, 59-61, 63, 66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lachenmeier et al. (Biotechniques, 1992;13(1):124-31; see whole document), and Pruitt (Gene, 1988; 66:121-34; see whole document) and further in view of Knappe et al. (US 5,989,867; see whole document).**

Additional embodiments are directed to the probes for the hybridization reaction comprising degenerate sequence. Lachenmeier et al., Pruitt and Rubenstein et al. do not explicitly teach that in a method where probes comprise degenerate sequence.

Knappe et al. teach a method for screening libraries by hybridization with degenerate probes to identify clones in different species of desired nucleic acid. (e.g. col. 29, ll. 10-21).

One of skill in the art would have been motivated to use degenerate probes or primers in order to isolate sequences related to a known sequence, such as other members of a gene family or sequences having single mutations, for example. At the time of invention it would have been prima facie obvious to substitute the specific probes taught by Lachenmeier et al. or Pruitt or Rubenstein et al. with such degenerate probes to recover ssDNA targets comprising related sequences. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of the Applicants' invention, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed. All art cited is already of record in the file.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER